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SOME RESULTS OF EPIDEMIOLOGICAL OBSERVATIONS WITH VACCINOPROPHYLAXIS OF TICK-BORNE ENCEPHALITIS

[Following is the translation of an article by S. S. Unanov, S. S. Magazannik, A. N. Oshchepkova, A. V. Shutov, Ye. I. Ioffe, A.L. Kameneva, A. S. Kursakova and P.S. Utnitskaya, Moscow Scientific-Research Institute of Viral Preparations, USSR Ministry of Public Health and the Sverdlovskaya Oblast Sanitary Epidemiological Station, published in the Russian-language periodical Voprosy Virusologii (Problems of Virology), No 4, 1965, pages 462--467. It was submitted on 23 Jul 1964. Translation performed by Sp/7 Charles T. Ostertag, Jr.]

In earlier published works [4, 5] we showed the harmlessness, non-reactogenicity, antigenic activity and epidemiological effectiveness of a tissue vaccine for the prophylaxis of tick-borne encephalitis. It was developed at the Moscow Scientific-Research Institute of Viral Preparations. However, these observations were carried out on a comparatively small scale. Together with this, in a significant number of patients with a diagnosis of tick-borne encephalitis laboratory investigations were not performed. This prevented the exposure of the true incidence of tick-borne encephalitis and did not permit an objective judgement of the vaccine.

In the present work we are presenting material from the study of the epidemiological effectiveness of the tissue encephalitis vaccine under the conditions of the mass vaccination in 1963.

Materials and Methods

The epidemiological test included the endemic rayons of Sverdlovskaya Oblast in which cases of tick-borne encephalitis are recorded every year. The formation of the test and control groups was carried out in conformance with the recommendations of WHO. There were no significant differences in the control and test groups based on occupation, age and social features. The potential threat of infection with tick-borne encephalitis was the same in both groups.

For the purpose of clearing up the risk of infection in small collectives detailed visits and interrogations of inhabitants were made to determine the degree of contact with ticks.

A special division of the work was devoted to the zoolog-parasitological observations. Constant observation was kept over ticks and their sources of nourishment in 3 different landscape zones: Mountain taiga, pine forests and forest steppes.

For the serological investigations of materials taken from patients or from persons suspected of having tick-borne encephalitis, and for determination of specific antibodies (virus neutralizing, hemagglutinating and complement fixing) we used the biological reaction of neutralization white mice with the RNV, RPGA and RSK.

In the RNV [Virus Neutralization Reaction] we used white mice weighing 8--10 grams. The sera from the patients was titrated with a 2-fold dilution, beginning with 1:4. To the titrated sera we added the virus in a dose of 100 LD₅₀. The mixture was shaken and set for contact for one hour at 37°. Each of the mice received 0.03 ml of the material intracerebrally. Four mice were used for each dilution of the serum. Observation was carried out for 14 days.

For the RPGA [passive hemagglutination reaction] the sera from the patients were preliminarily cleared of inhibitors and spontaneous agglutination by treating them with a 10% suspension of goose erythrocytes and a 25% solution of kaolin. The suspension of erythrocytes and the solutions of kaolin were prepared in a borate buffer solution at pH 9.0. The treated sera were titrated with a 2-fold dilution, beginning with 1:10. To the titrated sera we added an equal amount of antigen in a dose of 8 AU. The mixture from the sera and antigen was left for contact for 24 hours at 4°. Following contact we added an 0.5% suspension of goose erythrocytes, prepared in a phosphate buffer solution at pH 6.2. The results were considered after 45--60 minutes.

For the RSK [complement fixation reaction] we used the serum of guinea pigs, antigen, control immune and control normal sera, prepared by the Tomsk Scientific-Research Institute of Vaccines and Sera, sheep erythrocytes, hemolytic serum, and a physiological solution with pH 7.2--7.3. At first we titrated complement, diluted 10 times in a physiological solution. Two active doses were used in the reaction. Sera from patients were heated in a water bath at 56° for 30 minutes, then they were titrated with a 2-fold dilution, beginning with 1:4. To the titrated sera we added equal quantities of antigen and complement and left them for 18 hours at 4°. After contact, to each of the mixtures we added 0.4 ml of a hemolytic system, prepared from equal quantities of a 2.8% suspension of sheep erythrocytes in a physiological solution and hemolytic serum, after which the mixture was incubated at 37° up until distinct hemolysis in the controls, left at room temperature for 1½--2 hours and transferred to a refrigerator at 4°. The reaction was considered on the following day.

Results

In the epidemiological test the study of the tissue encephalitis vaccine was carried out on 401,416 men. Of these, 61,416 were vaccinated 3 times and 310,000 were not inoculated. The tissue vaccine was administered 3 times subcutaneously. The interval between the 1st and 2nd administration was 10 days, and the 3rd inoculation was performed in 3--4 weeks after the 2nd. The dose of vaccine for the 1st inoculation was 2 ml, and for the 2nd and 3rd -- 3 ml each. Students in the age group of 7--15 years were given 3 doses of 1 ml each of the vaccine.

A comparative study was made of the reactogenicity of 3 types of encephalitis vaccines: Tissue native, tissue dry and formalin cerebral. The general reactogenicity of the encephalitis preparations was studied by means of observations of inoculated persons for 7 days. The local reactions were considered in 12, 24, 48 and 72 hours after inoculation.

At the moment of administration of the vaccine or in several minutes after it, a fainting condition lasting 3--5 minutes was observed in a small group of inoculated persons. In those inoculated with tissue vaccine this occurred 6.3 times less often than in those inoculated with cerebral vaccine (table 1).

As can be seen from the data in table 1, the dried and native tissue vaccines were practically non-reactogenic. There is particular interest in the higher reactogenicity in those inoculated with the cerebral vaccine, in which the local and general reactions were noted 10--15 times more often in comparison with those inoculated with the tissue vaccine.

In the epidemic season of 1963, 205 cases of tick-borne encephalitis were recorded. We had 196 persons under observation.

During anamnesis in 170 persons tick bites were noted (86.8%), in 10 (5.1%) the source of infection was goat milk. In 8.1% of the cases the source of infection was not exposed.

The first cases of tick-borne encephalitis in 1963 were recorded in the beginning of May and coincided with the initial period of activity of ticks. An increase in the number of Ix. persulcatus ticks during the month of June corresponded with the maximum tick-borne encephalitis incidence.

The sharp lowering in the activity of ticks in August was in step with a drop in encephalitis incidence.

The data on tick-borne encephalitis incidence in Sverdlovskaya Oblast among inoculated and noninoculated persons are presented in table 2.

During the epidemic season of 1963 in the Verkhoturskiy and Novolyalinskiy epidemic foci (zone of forest mountains), incidence with tick-borne encephalitis in persons inoculated 3 times with tissue vaccine was 3.4 - 7.2 times lower than in noninoculated persons (see table 2).

Among the noninoculated persons the clinical diagnosis of tick-borne encephalitis was established in 189. The frequency index per 10,000 corresponded to 2.4, in inoculated persons it comprised 0.7.

The epidemiological effectiveness of the tissue vaccine comprised 3.4 with a 70% degree of protection of the population.

The great diversity of forms of tick-borne encephalitis causes significant difficulties in the diagnosis of this disease. Since it is known that among patients with an established diagnosis of tick-borne encephalitis there may be other nosological forms, during the epidemic season of 1963 we carried out laboratory investigations of cases of illness which were recorded as tick-borne encephalitis.

As diagnostic methods we used the neutralization reaction on mice, the RTCA [hemagglutination inhibition reaction] and the RSK.

All told 101 patients were investigated. The results of an analysis revealed a considerable difference in laboratory indices with a clinical diagnosis. In the RTCA 45.7% of the cases were confirmed. These results conformed with the data of the biological neutralization reaction. Complement fixing antibodies were exposed considerably less, which is appropriate for the existing concept concerning the lesser sensitivity of this reaction.

We carried out an analysis of incidence among inoculated and noninoculated persons. Only cases supported by laboratory data were taken into consideration. In table 3 we present the results of serological investigations of materials from patients with tick-borne encephalitis. In the group of noninoculated patients tick-borne encephalitis was documented in the laboratory in 45.7% of the cases, and in the noninoculated group -- in 57.1%. The indices of incidence per 10,000 among the inoculated and noninoculated comprised 0.4 and 1.4 correspondingly. The index of effectiveness equaled 3.5 while the coefficient of effectiveness was 71.4%.

The results for the reactogenicity and effectiveness of tissue encephalitis vaccine correspond to the data from other authors[1-3, 6].

In a statistical processing of the results obtained by the method of criterion of conformity and average error of difference, a reliability of data obtained was noted for the effectiveness of the tissue vaccine.

There was considerable interest in studying the clinical picture of tick-borne encephalitis among inoculated and noninoculated persons. An analysis of materials shows that in Sverdlovskaya Oblast, just as in previous years, there was a predominance of the meningeal form of the disease (60.1). In 9.6% of the patients a double wave course of the febrile period was noted. The meningeal symptoms were moderately expressed, pleocytosis was determined in the cerebrospinal fluid, and in a number of cases there was a moderate increase of protein (up to 1.0--1.2%). In 28.2% of the patients the acute phase of the disease proceeded severely, with expressed general cerebral symptoms, loss of consciousness and scattered symptoms of affection of the brain parenchyma.

Focal forms of the disease made up 11.9% of the cases, in 10.8% of the patients limp paresis developed, mostly in one arm. Attention is drawn to the appearance in 1963, just as in 1962, of individual cases of severe focal forms of the disease with an affection of the upper cervical section of the spinal cord and a syndrome of "drooping head", and affliction of the nuclei of the brain stem with a gradient course. Lethal cases were recorded among noninoculated persons.

Thus, in spite of the general lowering of incidence and the low mortality rate, there is a tendency for a certain increase in the clinical picture of tick-borne encephalitis.

A masked course of the disease was recorded in 18.1% of the cases. The disease developed following the bite of a tick and proceeded in the form of

a fever without distinct symptoms of an affliction of the nervous system. Thus, in a number of cases the results of the serological investigation did not confirm a diagnosis of tick-borne encephalitis and it was possible to assume that this was a neuroinfection of a different etiology.

In 7 of the vaccinated persons an increase of temperature was noted in 5-21 days following the bite of a tick. In 2 of the patients the fever was short-lived, there were no deviations on the part of the nervous system, and negative serological data did not permit a diagnosis of a masked form of tick-borne encephalitis. In 4 of the patients a meningeal form of the disease developed. It was of moderate severity with light meningeal symptoms and cellular-protein dissociation in the cerebral spinal fluid. In 1 patient a light poliomyelitis syndrome was revealed, with complete restoration of the affected function of the upper extremities after 2 months.

These materials testify to the lighter course of the disease in vaccinated persons. However, due to the scarcity of sick persons among the vaccinated group, it is difficult to make statistically reliable conclusions in concerning the clinical peculiarities of the course of illness in this group and among nonvaccinated persons.

In a comparison of the titer of antibemagglutinating and complement fixing antibodies in patients with focal forms of tick-borne encephalitis and following a meningeal syndrome or masked form of the disease, higher titers (up to 16 times) were noted in the latter.

Conclusions

1. In a comparative study of the reactogenicity of encephalitis preparations a non-reactogenicity is noted for the native and dried vaccines.

2. The distinct effectiveness of native tissue vaccine was observed in an extensive epidemiological experiment.

3. In 50% of the cases a clinical diagnosis of tick-borne encephalitis was not confirmed in the laboratory. Further observations and investigations are required for clearing up the nature of the disease.

Literature

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Table 1

Reactogenicity of various types of encephalitis vaccines (Fig. 2)

Type of vaccine	Local reaction (hyperemia, infiltrate)			General reaction	
	weak (up to 2.5 cm)	moderate (up to 5cm)	strong (more than 5cm)	Temperature up to 37.5-38.1°	fainting condition
Native tissue	0.1	0.01	-	0.01	0.3
Dried tissue	0.1	-	-	-	0.01
Cerebral	1.5	0.7	0.4	1.0	1.9

Table 2

Epidemiological effectiveness of tissue vaccine on the basis of clinical diagnosis

Rayon	Number observed		Number of cases of tick-borne encephalitis				Index of effectiveness	Coefficient of effectiveness	Index	
	Inoculated	Noninoculated	Inoculated		Noninoc.				χ^2	t
			abs.	per 10000	abs.	per 10000				
Novolyalinskiy	3 285	6 000	2	6.0	26	43.3	7.2	65.0	9.7	9.3
Verkhoturskiy	2 683	2 800	5	18.6	18	64.2	3.4	70.0	6.0	4.7
All told in Sverdlovskaya Oblast	91 416	738 717	7	0.7	189	2.4	3.4	70.0	11.2 ²	54.6

* $P < 0.01$ 2 $P < 0.001$

Table 3

Epidemiological effectiveness of tissue vaccine on the basis of laboratory confirmed cases

Group investigated	Number under observation	Number investigated in the laboratory	Number of laboratory confirmed diagnoses		Index per 10 000	Index of effectiveness	Coefficient of effectiveness (in %)	Index	
			abs.	%				χ^2	t
Inoculated	91 416	7	4	57.1	0.4	3.5	71.4	5.4 *	35.7
Noninoculated	310 000	94	43	45.7	1.4				

* $P = 0.01$